# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference MG/PB60227/PCT | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No. PCT/EP2004/004245 | International filing date *(day/month/year)* 21.04.2004 | Priority date *(day/month/year)* 23.04.2003 |

International Patent Classification (IPC) or national classification and IPC
C07D401/04, C07D211/62, C07D417/04, C07D401/14, C07D405/14, C07D401/06, C07D413/10, C07D413/04, C07D417/10, C07D401/10, C07D413/14, C07D417/14, A61K31/496, A61K31/506, A61K31/501, A61K31/497, A61P25/28

Applicant
GLAXO GROUP LIMITED et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 14.12.2004 | 18.07.2005 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Helps, I<br>Telephone No. +49 89 2399-8209 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/004245

## Box No. I Basis of th rep rt

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   **Description, Pages**

   1-78 as originally filed

   **Claims, Numbers**

   1-29 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**Box No. III Non- stablishm nt f pinion with regard to nov lty, inventive st p and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 27(part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 27 (part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-29 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-29 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-26, 28, 29 |
| | No: | Claims | 27 see below |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

V. CITATIONS AND EXPLANATIONS

The following documnets are mentioned in this report.

| | |
|---|---|
| WO-A-02 47679 | (A) |
| US-A1-2003/073718 | (B) |
| US-A-6,093,718 | (C ) |
| WO-A-2003 004480 | (D) |
| WO-A-02 32893 | (E) |

The novel structural feature of the compounds of claim 1 is the R3 substituent, which represents C3-8 alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl or cycloalkylalkyl, on the piperazine ring. The dependent claims 2-22, as well as claim 23 drawn to pharmaceutical compositions containing compounds of claim 1, claims 24 and 25 drawn to compounds of claim 1 for use in therapy, claim 26 drawn to the use of compounds of claim 1 for the manufacture of medicaments, claim 27 drawn to methods of treatment using compounds of claim 1, claim 28 drawn to pharmaceutical compositions containing compounds of claim 1 for use in therapy, and claim 29 drawn to processes for the preparation of compounds of claim 1 are novel by consequence. Claims 1 to 29 therefore meet the Novelty requirements of Article 33(2) PCT.

Document (A) describes 1-(1-(2-nitrophenyl)-piperidin-4-yl)-carbonyl-4-methyl piperazine and its corresponding 2-aminophenyl derivative (see page 84, line 18 to page 85, line 11). Compounds under the scope of claim 1 of the present application can be reached from these compounds by replacing the 4-methyl group by a C3-8 alkyl group. However, the compounds of (A) cited above are intermediate compounds for the preparation of vasopressin receptor antagonists, and their use as histamine H3 receptor antagonists is not suggested. Document (B) describes 1-aryl-4-(1-aryl-piperidin-4-ylcarbonyl)-piperazines in which said 1-aryl-piperidine group is substituted by a 4-hydroxyaminocarbonyl-pyran-4-yl group. Compounds under the scope of the present application could be reached from these compounds by replacing the aryl group at the 1-position of the piperazine by an R3 group as defined in claim 1. However, the compounds of (B) are matrix metalloproteinase inhibitors and their use as histamine receptor antagonists is not suggested. Also, the compounds of document (C ) are squalene cyclase inhibitors and their use as histamine

H3 receptor antagonists is not suggested.

Document (D) describes histamine H3 antagonists based on 1-cycloalkyl (or 1-alkyl)- 4-(4-phenylcyclohexylcarbonyl)-piperazines (see examples 127, 159 and 242). Compounds under the scope of the present application can be reached from these compounds by replacing the cyclohexyl ring carbon atom bound to the phenyl group by nitrogen. However, this would not be an obvious structural replacement for the skilled man to consider when investigating the preparation of further histamine H3 antagonists. The histamine He receptor antagonists of document (E), being based on N-arylmethyl-4-(methoxyimino pyridin-2-ylmethyl)-piperidin-1-carbonyl piperidines, are also not considered to be structurally close to the presently claimed compounds.

Inventive step (Article 33(3) PCT) can be recognised because the problem of making available further histamine He receptor antagonists for the treatment of neurological and psychiatric disorders has been solved in a non obvious manner.

For the assessment of the present claim 27 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PB60227

**Description 39**

**5-(4-Bromophenyl)-3-methyl isoxazole (D39)**

A solution of n-BuLi (81ml of a 1.6M solution in hexanes) was added to a solution of acetone oxime (4.85g) in THF (100ml) at 0°C. The reaction mixture was allowed to warm to rt over 1h. A solution of methyl 4-bromobenzoate (9.4g) in THF (30ml) was then added to the reaction mixture and allowed to stir for 24h. Water (50ml) was added to the reaction, the organics were extracted and evaporated to give a brown oil, which was further evaporated from toluene (2x25ml). The crude product was purified by column chromatography (silica gel, 10-25% gradient of EtOAc in hexane) to give the title compound (D39) as a pale yellow solid (5.4g). LCMS electrospray (+ve) 239 ($MH^+$).

**Description 40**

**3-(4-Bromophenyl)-5-methyl-1,2,4-oxadiazole (D40)**

**Step 1: 4-Bromo-N-hydroxy-benzenecarboximidamide**

4-Bromophenylcarbonitrile (10.2g), hydroxylamine hydrochloride (7.8g) and $Et_3N$ (11.3g) were dissolved in EtOH (250ml) and the reaction mixture was heated at reflux for 3h, after which it was evaporated to form a white precipitate of the desired amidoxime, which was filtered off and washed with water (25ml). The filtrate was extracted into EtOAc (2x25ml), and the combined organic extracts were dried ($Na_2SO_4$) and evaporated to give a second crop of the subtitle compound (combined yield = 11.1g). LCMS electrospray (+ve) 216 ($MH^+$).

**Step 2: 3-(4-Bromophenyl)-5-methyl-1,2,4-oxadiazole**

The product from D40, step 1 was suspended in acetic anhydride and heated to 100°C for 4h, then 120°C for 3h. After cooling the reaction mixture was evaporated to give a brown solid. This was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The organic phase was washed with saturated aqueous NaCl, dried ($Na_2SO_4$) and evaporated to give a yellow solid. The crude product was purified by column chromatography (silica gel, 10-100% gradient of EtOAc in hexane) to give the title compound (D40) as a white solid (6.2g). LCMS electrospray (+ve) 240 ($MH^+$).

**Description 41**

**5-(4-Bromophenyl)-3-methyl-1,2,4-oxadiazole (D41)**

N,N-dimethylacetamide dimethyl acetal

4-Bromobenzamide (5.3g) and ~~dimethylformamide dimethoxyacetal~~ (35ml) were heated together at 125°C for 2h. The reaction was allowed to cool to rt and the liquid evaporated to give a pale yellow solid. Hydroxylamine hydrochloride (2.2g) in 1N NaOH solution (36ml) was added, followed by dioxane (36ml) then AcOH (48ml). The reaction mixture was stirred at rt for 30min then heated at 90°C for 3h. The reaction was allowed to cool to rt and saturated aqueous $K_2CO_3$ solution (100ml) was added followed by DCM (200ml) before filtering. The organic phase was separated from the mixture, then saturated brine (100ml) was added and the aqueous phase was extracted into EtOAc (200ml). The combined organic phases were dried ($Na_2SO_4$) and evaporated to give a